Modulation and regulation of intracellular pH in healthy human brain studied by means of Chemical Exchange Saturation Transfer (CEST) at 7T

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Abstract. pH homeostasis is vital to normal functioning of cells. ^{31}P Magnetic Resonance Spectroscopy (^{31}P MRS) is currently a gold standard for the non-invasive measurements of intracellular pH (pHi) using inorganic phosphate (Pi) as a probe. However, this method suffers from low resolution and limited pH sensitivity. The purpose of this work was to show that Amide Proton Transfer (APT) imaging is a great alternative to ^{31}P MRS offering both high resolution and pH sensitivity.

Methods. All experiments were carried out on a 7T whole body MR system (Philips, Best, the Netherlands) using a 32 channel transmit-receive head coil for CEST and a coil for ^{31}P MRSI (MR Coils BV, Drunen, The Netherlands). 6 volunteers participated in the experiments (3 for hypocapnia and 3 for hyperventilation). Brain pH was modulated using Respiract (Thornhill Reasearch Inc., Toronto, Canada) by changing PCO_2 (+10 mmHg and -10 mmHg for hypocapnia and hyperventilation, respectively) from the baseline level (**Fig. 1**). The challenge duration was 4 min for hypocapnia and 8 min for hyperventilation. The CEST sequence (B_1 2.3μT for hypocapnia and 1 μT for hypeventilation) used was published earlier [1]. Asymmetry was calculated as MTRasym=CEST(-ώ ppm)/M_0-CEST(ώ ppm)/M_0 in the region from 3 to 4 ppm from the whole brain averaged for white matter (WM) and gray matter (GM) using their binary masks and corrected for variations in B0 and B1. A B_1map was acquired based on a dual TR sequence [2]. A T_1-weighted anatomical scan (3D TFE, TR/TE/FA= 5.5ms/2.0ms/6°, voxel size 1mm) was used for co-registration of the CEST data and B_1map. The anatomical scan was used to create masks of WM and GM from their partial volume masks using a fixed threshold. 3D ^{31}P chemical shift imaging (CSI, 25x25x25mm^3, 5min) was performed to measure pH using Pi as a probe: 3.27 ppm (Pi acidic form), 5.69 ppm (Pi basic form) and PCr (phosphocreatine) as a reference (6.72 pKa). Both co-registration and segmentation were done in FSL (FMRIB v6.0, UK). All data analysis was done in MATLAB®.

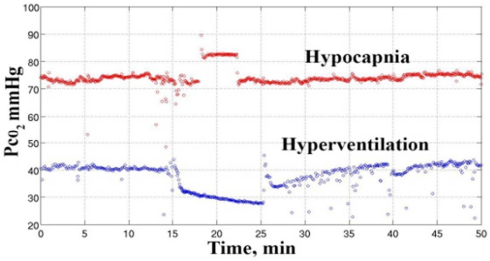
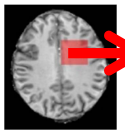


Fig. 1. Traces of partial pressure of CO_2 vs time for two challenges: hypocapnia (top) and hyperventilation (bottom). Hypocapnia trace was shifted by 40 mmHg.

Results and discussion.

pH modulations in vivo in response to different breathing patterns were measured by ^{31}P (**Fig. 2**). Both hypocapnia and hyperventilation induced pH change was estimated to be ~0.1pH units. This pH change corresponds to a 10mmHg change in PCO_2. Thus, average brain buffering capacity is approximately 100mmHg (PCO_2)/pH. However, the low spatial resolution of ^{31}P does not allow estimating buffering capacity of WM distinctively from GM in vivo. High resolution APT imaging was used to get an estimate on buffering capacity of different brain compartments, i.e. WM and GM. Although MTRasym is heavily NOE (Nuclear Overhauser Enhancement)-weighted, since NOE is not pH dependent [3] all variation in MTRasym is expected due to pH sensitive APT effect. MTRasym comparison reveals higher sensitivity of WM to hyperventilation challenge (**Fig. 3 A**) compared to GM ($p<0.01$). The slopes from normal (1) to hyperventilation (2) breathing pattern were 30.3 and 142.93mmHg (PCO_2)/MTRasym for WM and GM, respectively. The slopes from hyperventilation (2) to recovery (3) breathing pattern were 76.9 and 111.1 3mmHgPCO_2)/MTRasym for WM and GM, respectively. The difference in the 1 to 2 breathing pattern slope is most likely a result of different buffering mechanisms in WM and GM in response to alkalosis. Both WM and GM show very similar sensitivity to hypocapnia challenge (**Fig. 3 B**). Slopes 1 to 2 and 2 to 3 breathing patterns were 58.8/40.0 mmHg (PCO_2)/MTRasym and 27.8/15.8mmHg (PCO_2)/MTRasym for WM and GM, respectively. The results suggest that GM and WM have similar mechanism to counter acidosis. The slopes give an estimate about WM and GM buffering capacity in healthy human brain.



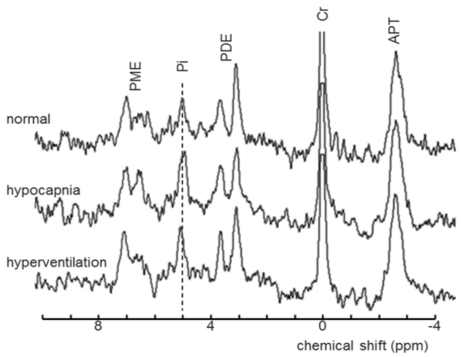


Fig. 2. 31P spectra from a healthy human brain during normal breathing pattern (top), hypocapnia (middle) and hyperventilation (bottom). The vertical dashed line represents the position of Pi during normal breathing pattern. APT (adenosine triphosphate), Cr (phosphocreatine), PDE (phosphodiesters), Pi (inorganic phospate) and PME (phosphomonoesters).

Conclusions. The work shows that APT imaging can be used to estimate pH buffering capacity of different brain compartment. The findings of this study suggest that WM has higher than GM sensitivity to hyperventilation challenge probably due to different anti-alkalosis buffering mechanism. On the other hand, both WM and GM had similar response to hypocapnia challenge, assuming similar anti-acidosis buffering mechanisms.

References. [1] Jones CK et al. MRM 2012. [2] Yarnykh VL. MRM. 2007. [3] Jin T et al. MRM 2013.**This work was funded by the European Commission (FP7-PEOPLE-2012-ITN-316716).**

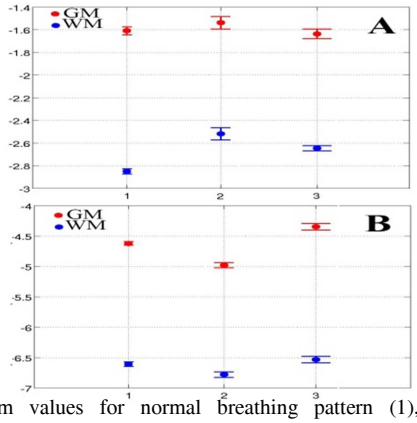


Fig. 3. MTRasym values for normal breathing pattern (1), challenge (2): hyperventilation (A) and hypocapnia (B) and post challenge normal breathing pattern after 10min recovery (3).